

II. REMARKS

A. Introduction

Applicants submit this Preliminary Amendment in a bona fide attempt to (i) advance the prosecution of this case, (ii) answer each and every ground of rejection as set forth in the Final Action, dated July 2, 2002, and (iii) place the claims in a condition for allowance.

As indicated above, Applicants have amended Claims 1-7, 9, 12-13, 19 and 21-23 and deleted Claims 14-18, 20 and 24. Applicants have also added new Claims 25-29.

Attached hereto is a marked-up version of the changes made to the claims by the current amendments. The attached page is captioned "**Version With Markings To Show Changes Made.**"

Applicants respectfully submit that the noted amendments (and new claims) merely make explicit that which was (and is) disclosed or implicit in the original disclosure. The amendments thus add nothing that would not be reasonably apparent to a person of ordinary skill in the art to which the invention pertains.

B. Response to Rejections

1. 35 U.S.C. § 112

In the Final Action, dated July 2, 2002, the Examiner rejected Claims 20 and 24 under 35 U.S.C. § 112 as being "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention". The Examiner contended:

"The expression 'therapeutically stable' in claims 20 and 24 is a relative term which renders the claim indefinite. The expression 'therapeutically stable' is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree."

Applicants have accordingly deleted Claims 20 and 24.

2. 35 U.S.C. § 103(a)

The Examiner also rejected Claims 1-24 under 35 U.S.C. § 103(a) as being unpatentable "over Hill (WO 92/14472 from the Information Disclosure Statement received April 20, 2001) and Gordon (Clinical therapeutics, 1998; 20(1): 26-39) in view of Richards (U.S. Patent 4,985,418), references of record in the previous office action mailed July 18, 2001, and Budavari

(Merck Index 11th ed. 1989, monograph 6021 and 7879).” The Examiner contended, *inter alia*:

“Hill teaches a topical composition employing 0.05% of the corticosteroid, fluticasone propionate, 10.00% of cetostearyl alcohol, 10% of White Soft Paraffin, 2.50 of Polysorbate 60, 10.00% of propylene glycol, and purified water (see particularly Example 1). Hill also teaches that the topical composition is prepared by mixing the ingredients and melting the mixture and then cool the mixture down (See particularly page 2, third paragraph). Hill also teaches that the topical composition is useful in treating skin conditions including inflammation (See particularly page 1, 6th paragraph).

Gordon teaches a corticosteroid containing composition, free of mineral oil and white soft paraffin, employing Cetostearyl alcohol, cetomacrogol 1000, Isopropyl myristate, propylene glycol, Dimethicone 360, citric acid, sodium citrate, imidurea, and water (see page 28, table 1).”

Although the Examiner recognized that “[t]he references do not expressly teach [Applicants’] composition as free of mineral oil and white soft paraffin”, the Examiner contended:

“One of ordinary skill in the art would have been motivated to formulate a topical fluticasone composition, as free of mineral oil and white soft paraffin, with the excipient ingredients in the amount herein. Possessing the teachings of the Gordon, one of ordinary skill in the art would be reasonably expected to successfully formulate any corticosteroid topical composition such as fluticasone cream as free of mineral oil and white soft paraffin.”

It is well established that in determining what is and what is not obvious under § 103, all properties and advantages not in the prior art must be considered. See *In re Wright*, 848 F.2d 1216, 6 U.S.P.Q. 2d 1959, 1962 (Fed. Cir. 1988) (“Factors including unexpected results, new features, solution of a different problem, novel properties, are all considerations in the determination of obviousness in terms of 35 U.S.C. § 103”). Indeed, it is the invention as a whole, including distinct functions that must be considered in obviousness determinations.

It is further well established that obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or motivation supporting the combination. See *ACS Hospital Systems, Inc. v. Monteflore Hospital*, 732 F.2d 1572, 1577, 221 U.S.P.Q. 929, 922 (Fed. Cir. 1984). Further, although obviousness

does not require absolute predictability, a reasonable expectation of success is necessary. See *In re Clinton*, 527 F.2d 1226, 1228, 188 U.S.P.Q. 365, 367 (CCPA 1976).

As set forth above, independent Claims 1 and 2, have been amended to provide for a fluticasone based topical lotion having a decreased concentration of occlusive agent, i.e., “less than about 5.0 wt.% of an occlusive agent selected from the group consisting of mineral oil and white soft paraffin.” Independent Claims 12 and 13 have also been amended to provide for a fluticasone based topical lotion devoid of the occlusive agent.

As noted by the Examiner, “[t]he references do not expressly teach [Applicants’] composition as free of mineral oil and white soft paraffin.” Indeed, not only do the references **not** teach or suggest Applicants’ compositions, the references also **do not** teach or suggest the elimination of the occlusive agent, i.e., mineral oil and white soft paraffin, to enhance the vasoconstrictor potency of the fluticasone contained in the composition. Moreover, the references do not provide any motivation to eliminate the occlusive agent.

As the Examiner has also noted, Gordon merely “teaches a corticosteroid containing composition, free of mineral oil and white soft paraffin, employing Cetostearyl alcohol, cetomacrogol 1000, isopropyl myristate, propylene glycol, Dimethicone 360, citric acid, sodium citrate, imidurea and water” to enhance the moisture content in treated skin. Indeed, the only reference to an occlusive agent is set forth on p. 30:

In general, the effectiveness of an emollient increases with its degree of occlusiveness. Occlusiveness is an emollient’s ability to create a barrier that keeps moisture from leaving the skin. Agents that have occlusive properties (many of which have emollient properties as well) include petrolatum, oils of vegetable and animal origin, glycerin, and fluid silicone or dimethicone.

Gordon is thus devoid of any reference to vasoconstrictor potency.

Even if, *in arguendo*, the Gordon composition were deemed a fluticasone based composition, the *apparent* elimination of the occlusive agent, i.e., mineral oil/white soft paraffin, carries with it **no** reasonable expectation that the elimination of the occlusive agent would enhance the vasoconstrictor potency of fluticasone.¹ Thus, at best, the Gordon reference is

¹ Applicants further submit that on information and belief, the elimination of the occlusive agent in the Gordon compositions would have little, if any, effect on the vasoconstrictor activity.

merely a suggestion for “virtually endless experimentation” and, hence, does not establish *prima facie* obviousness. See *In re Dow Chemical*, 837 F.2d 469, 473, 5 U.S.P.Q. 2d 1529, 1532 (Fed. Cir. 1989). *In re Geiger*, 815 F.2d 686, 688, 2 U.S.P.Q. 2d 1276, 1278 (Fed. Cir. 1987) (“At best, in view of these disclosures, one skilled in the art might find it obvious to try various combinations of these known scale and corrosion prevention agents. However, this is not the standard of 35 U.S.C. § 103.”); Accord, *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q. 2d 1596 (Fed. Cir. 1988).

As explicitly set forth in the specification, the topical lotions of the invention provide increased vasoconstrictor potency of fluticasone as compared to well known, prior art fluticasone creams.

“The fluticasone lotion of the present invention has proven to be unexpectedly superior in terms of efficacy and safety. Evaluations were performed using the Vasoconstrictor Assay. Evaluations also used a human model to predict clinical potency of corticosteroids in (1) controlled efficacy and safety trials and (2) subjects with a corticosteroid-responsive dermatosis, atopic dermatitis. Safety and efficacy evaluations were performed on the fluticasone lotion 0.05% by applying the lotion extensively to all body regions: head and neck (including face,) trunk, upper limbs and lower limbs.

The potency of the fluticasone lotion, as determined by the Vasoconstrictor Assay, was greater than mid-potency fluticasone cream (CUTIVATE™ Cream). The potency of the fluticasone lotion was less than the high-potency corticosteroid preparations. Application of the lotion formulation over 4 weeks resulted in a superior adverse event profile devoid of commonly encountered side effects encountered using corticosteroids in the mid-to-high potency range.” p.15, ll. 9-23.

Applicants submit that the Vasoconstriction Assay or Test (VC) is widely accepted at the human bioassay in drug development to (i) assess the topical pharmacologic potency of various corticosteroid drugs for screening potential drug candidates, (ii) screen candidate formulations for optimized potency in the formula selection process, and (iii) establish the potency class of commercial topical corticosteroid drug products.

Applicants further submit that the well established and recognized method of conducting the bioassay is with reference products with known vasoconstriction potency. As is well known

in the art, the same compound (drug substance) is typically the primary standard in the vehicle most similar to the test product, and frequently products in higher and lower potency categories are used to validate the experiment. See *Topical Corticosteroids, Guidelines for Therapy*, Hoechst-Roussel Pharmaceuticals Inc., pp. 24-25, attached in Appendix A.

It is also recognized that the bioassay is a clinical test with some variability due to differences in subject's potential for skin blanching. Thus, the test is commonly judged by rank order, relative to products of established potency.

Referring now to Table 1 in the specification, Applicants submit that the noted differences between the lotion formulations and cream are clearly not random chance, since each of the two lotion formulations was more potent than the cream, i.e., 33% and 25%, respectively. The Examiners comments relating to "statistical error" is thus not relevant given the magnitude of difference and the replication of the results with more than one lotion formulation.

The significance of the data is further confirmed in Table 2, wherein commercially available corticosteroid products from different known potency classes are compared. As will be readily appreciated by one having ordinary skill in the art, the rank order is consistent with accepted potency classification and published data. See *Potency Rankings of Topical Corticosteroids*, attached in Appendix B.

Applicants further submit that Cutivate (fluticasone) Cream is the closest prior art, since it contains the same drug molecule. Further, the cream dosage form is the closest possible dosage form to the lotion, since it is a similar oil-in-water emulsion.

The next closest prior art is Cutivate (fluticasone) Ointment, which is the same corticosteroid in a totally different dosage form. The ointment is organic based and not an emulsion.

The composition of Cutivate Cream is set forth in the specification on page 1, lines 14 through 16, as follows:

INGREDIENTS	Cutivate Cream	Cultivate Cream	Cutivate Lotion in specification: (ex 1)	(ex 2)	(pg. 17)
Fluticasone propionate	0.05%	0.05%	0.05%	0.05%	0.05%
Propylene glycol	yes	yes	10.00%	0.00%	10.00%
Mineral oil	yes	yes	0.00%	0.00%	0.00%
Cetostearyl alcohol	yes	yes	5.00%	5.25%	5.00%
Ceteth-20	yes	yes	0.00%	0.75%	0.00%
Isopropyl myristate	yes	yes	1.00%	2.00%	1.00%
Cetomacrogol 1000	no	no	1.00%	0.00%	1.00%
Dimethicone 360	no	no	1.00%	0.00%	1.00%
Buffers	yes	---	---	---	---
Citric acid	---	yes	0.05%	0.05%	0.05%
Sodium Citrate	---	no	0.08%	0.00%	0.08%
Dibasic Sod Phosphate	---	yes	0/00%	0.06%	0.00%
Preservatives	yes	---	---	---	---
Imidurea	---	yes	0.30%	0.20%	0.14%
Methylparaben	---	no	0.20%	0.20%	0.17%
Propylparaben	---	no	0.10%	0.10%	0.06%
Purified Water	balance	balance	balance	balance	balance

** PI refers to the commercial product Package Insert (the product literature).

Thus, as can be seen, the compositions of the Cutivate Lotion are quite comparable to the prior art cream. There is, however, a very notable physical appearance of the lotion versus cream in consistency (viscosity), i.e., the cream is thicker (much more viscous). This is why the results are so unexpected.

Furthermore, it is well known that propylene glycol very often can enhance vasoconstriction activity of corticosteroids in topical formulations. However, Applicants have found that the inclusion of propylene glycol in the topical lotions of the invention unexpectedly has no effect on the vasoconstriction activity (e.g., the 6% difference in the vasoconstriction scores of 28.4 for the propylene glycol-containing formulation compared and 26.7 for the propylene glycol-free formula from Table 1). Thus, the published teaching on steroid topical corticosteroid enhancement through formulation with propylene glycol, as is used in the commercial fluticasone cream formula, teaches away from the topical lotions of the invention.

With regards to Table 2, Applicants submit the following points of clarification: First, the potency of Temovate Cream is Very High, rather than High. Second, Cutivate Cream (fluticasone Cream 0.05%) is the only test material in the experiment intended to represent closest prior art.

As will be appreciated by one having ordinary skill in the art, Temovate Cream is a very high potency topical corticosteroid. Indeed, it is the most potent known. Therefore, it was included in the experiment to validate the experiment by showing separation from fluticasone lotion and reproduction of the published rank order of the control products used in the experiment.

Elecon Lotion is similarly known to be a high potency product. One would thus expect Cutivate lotion to be of the same potency of the cream. Hytone (hydrocortisone) Lotion was included in the experiment because it is known to be in the lowest potency class among topical corticosteroids. It is in fact the only topical corticosteroid approved for sale without a prescription up to 1% strength.

Copies of the Physicians' Desk Reference monographs for the noted compounds are attached in Appendix C.

As will be appreciated by one having ordinary skill in the art, the test results set forth in Table 2 are consistent with the literature and as expected, with the exception of the higher potency of the fluticasone based lotions of the invention compared to Cutivate (fluticasone Cream (@ 0.05%).

Applicants thus respectfully submit that Claims 1-7, 9, 12-13, 19 and 21-23, as amended, define an invention that is unobvious over the cited references. Indeed, the references neither teach or suggest Applicants' compositions, nor the elimination of mineral oil and white soft paraffin to enhance the vasoconstrictor potency of the fluticasone contained in the composition. Claims 1-7, 9, 12-13, 19 and 21-23, and new Claims 25-29 should thus be allowed.

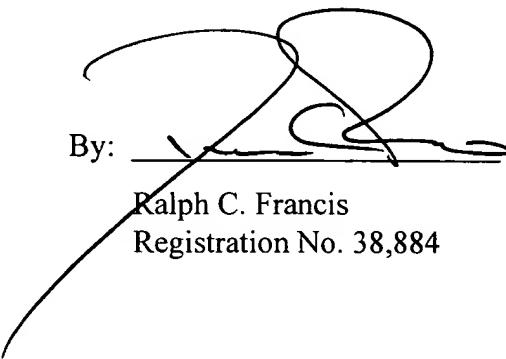
Applicants have also reviewed the prior art made of record and not relied upon by the Examiner and has found them not to teach or make obvious the present invention.

III. CONCLUSION

Applicants having answered each and every ground of rejection as set forth by the Examiner in the Final Action, dated July 2, 2002, and having added no new matter, believe that this response clearly overcomes the references of record, and now submit that all claims in the above-referenced patent application are in condition for allowance and the same is respectfully solicited.

Respectfully submitted,

FRANCIS LAW GROUP

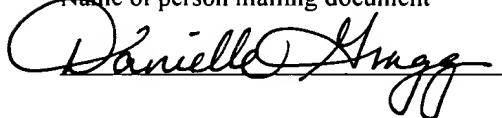
By: 

Ralph C. Francis
Registration No. 38,884

December 24, 2002
1808 Santa Clara Ave
Alameda, CA 94501
(510) 769-9800

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Danielle Gragg
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VERSION WITH MARKINGS TO SHOW CHANGES**In the claims:**

Claims 14-18, 20 and 24 have been deleted.

Claims 1-7, 9, 12-13, 19 and 21-23 have been amended as follows:

1. (Amended) A topical lotion, comprising:
about 0.005 to 1.0 wt.% fluticasone, or a pharmaceutically acceptable salt or ester thereof;
about 1.0 to 10.0 wt.% of a C₁₄-C₂₀ fatty alcohol or mixtures thereof;
about 1.0 to 5.0 wt.% of at least one first skin conditioning agent;
about 5.0 to 15.0 wt.% propylene glycol;
up to about[10.0] 5 wt.% of an occlusive agent selected from the group consisting of mineral oil [or] and white soft paraffin; and
the balance in water.
2. (Amended) A topical lotion, comprising:
about 0.005 to 1.0 wt.% fluticasone propionate;
about 3.0 to 7.0 wt.% of a C₁₄-C₂₀ fatty alcohol, or mixtures thereof;
about 0.5 to 3.0 wt.% of at least one first skin conditioning agent;
about 0.25 to 2.0 wt.% of at least one surfactant;
about 7.0 to 12.0 wt.% propylene glycol;
up to about [10] 5 wt.% of an occlusive agent selected from the group consisting of mineral oil [or] and white soft paraffin; and
the balance in water.
3. (Amended) The lotion [according to claim] of Claim 1, further comprising [less than] up to about 5.0 wt.% dimethicone.
4. (Amended) The lotion [according to claim] of Claim 2, further comprising [less than] up to about 5.0 wt.% dimethicone.
5. (Amended) The lotion [according to claim] of Claim 1, wherein said pharmaceutically acceptable ester of fluticasone [is] comprises fluticasone propionate.

6. (Amended) The lotion [according to claim] of Claim 1, comprising:
about 0.05 wt.% fluticasone propionate[,];
about 5.0 wt.% cetostearyl alcohol[,];
about 1.0 wt.% isopropyl myristate[,];
about 1.0 wt.% dimethicone[,];
about 1.0 wt.% cetomacrogol[,];
about 10.0 wt.% propylene glycol;
less than about 0.30 wt.% imidurea[,];
less than about 0.20 wt.% methyl paraben[,];
less than about 0.10 wt.% propyl paraben[,];
[about 0.05 wt.% citric acid (anhydrous),
about 0.08 wt.% sodium citrate, and];
a preservative effective amount of imidurea, methyl paraben, and propyl paraben;
a buffering effective amount of anhydrous citric acid and sodium citrate; and
the balance in purified water.
7. (Amended) The lotion [according to claim] of Claim 1, comprising:
about 0.05 wt.% fluticasone propionate[,];
about 5.25 wt.% cetostearyl alcohol[,];
about 2.0 wt.% isopropyl myristate[,];
about 10.0 wt.% propylene glycol[,];
about 0.20 wt.% imidurea[,];
about 0.20 wt.% methyl paraben[,];
about 0.10 wt.% propyl paraben[,]; and
the balance in purified water.
9. (Amended) The lotion [according to claim] of Claim 2, [having the formula]
comprising:
about 5.25 wt.% cetostearyl alcohol[,];
about 2.0 wt.% isopropyl myristate[,];
about 10.0 wt.% propylene glycol[,];
about 0.20 wt.% imidurea[,];
about 0.20 wt.% methyl paraben[,];

about 0.10 wt.% propyl paraben[,]; and
the balance in purified water.

12. (Amended) [The] A topical lotion [according to claim 1, free of mineral oil or white soft paraffin.] comprising:

about 0.005 to 1.0 wt.% fluticasone or a pharmaceutically acceptable salt or ester thereof;

about 1.0 to 10.0 wt.% of a C₁₄-C₂₀ fatty alcohol or mixtures thereof;
about 1.0 to 5.0 wt.% of at least one first skin conditioning agent;
about 5.0 to 15.0 wt.% propylene glycol; and,
the balance in water.

13. (Amended) [The] A topical lotion [according to claim 2, free of mineral oil or white soft paraffin.] comprising:

about 0.005 to 1.0 wt.% fluticasone propionate;
about 3.0 to 7.0 wt.% of a C₁₄-C₂₀ fatty alcohol, or mixtures thereof;
about 0.5 to 3.0 wt.% of at least one first skin conditioning agent;
about 0.25 to 2.0 wt.% of at least one surfactant;
about 7.0 to 12.0 wt.% propylene glycol; and,
the balance in water.

19. (Amended) The topical lotion of [claim 18] Claim 12, wherein [the] said lotion has a 2-hour mean blanching score of at least about 2.1[, an AUC of at least about 26.7] and an average mean blanching of at least about 1.5.

21. (Amended) A method of treating a skin condition, comprising the steps of providing a topical lotion, [including] said topical lotion comprising about 0.005 to about 1.0 wt.% fluticasone, or a pharmaceutically acceptable salt or ester thereof; about 1.0 to about 10.0 wt.% of a C₁₄-C₂₀ fatty alcohol or mixtures thereof; about 1.0 to about 5.0 wt.% of at least one skin conditioning [agents] agent; about 5.0 to about 15.0 wt.% of propylene glycol; [less than about 10.0 wt.% of mineral oil or white soft paraffin,] and the balance in water; and[,] applying [the] said lotion to [the skin having the] said skin condition.

22. (Amended) The method of [claim] Claim 21, wherein [the] said skin condition is selected from the group consisting of corticosteroid-responsive dermatosis, atopic dermatitis, inflammation, eczema, erythema, papulation, scaling, erosion, oozing, crusting [or] and pruritis.

23. (Amended) The [topical lotion] method of [claim] Claim 21, wherein [the] said topical lotion has a 2-hour mean blanching score of at least about 2.1[, an AUC of at least about 26.7,] and an average mean blanching of at least about 1.5.

New Claims 25-29 have been added:

25. (New) The topical lotion of Claim 1, wherein said lotion has a 2-hour mean blanching score of at least about 2.1 and an average mean blanching of at least about 1.5.

26. (New) The topical lotion of Claim 2, wherein said lotion has a 2-hour mean blanching score of at least about 2.1 and an average mean blanching of at least about 1.5.

27. (New) The topical lotion of Claim 13, wherein said lotion has a 2-hour mean blanching score of at least about 2.1 and an average mean blanching of at least about 1.5.

28. (New) A topical lotion comprising:

about 0.005 to 1.0 wt.% fluticasone, or a pharmaceutically acceptable salt or ester thereof;

about 1.0 to 10.0 wt.% of a C₁₄-C₂₀ fatty alcohol or mixtures thereof;

about 1.0 to 5.0 wt.% of at least one skin conditioning agent;

about 5.0 to 15.0 wt.% propylene glycol; and

the balance in water.

29. (New) A topical lotion comprising:

about 0.005 to 1.0 wt.% fluticasone;

about 3.0 to 7.0 wt.% of a C₁₄-C₂₀ fatty alcohol or mixtures thereof;

about 0.5 to 3.0 wt.% of at least one skin conditioning agent;

about 0.25 to 2.0 wt.% of at least one surfactant;

about 7.0 to 12.0 wt.% propylene glycol; and

the balance in water.

Appendix A

Topical Corticosteroids

Guidelines for Therapy

Hoechst 

Hoechst-Roussel Pharmaceuticals Inc.
Somerville, New Jersey 08876



Roger C. Cornell, M.D.

born in 1938, graduated from Stanford University Medical School in 1964. 1964-1965 internship in the New York Hospital. Until 1969 in the Air Force. 1969-1970 Resident in internal medicine, 1970-1973 in dermatology at the University Hospital San Diego, California. Since 1972 at the Scripps Clinic and Research Foundation, since 1977 Head, Division of Dermatology. Since 1981 Associate Clinical Professor of Dermatology at the University Hospital San Diego, California. Chairman of Academic Affairs of the Scripps Clinic and Research Foundation.



Richard B. Stoughton, M.D.

born in 1923, graduated from University of Chicago Medical School in 1947. 1947-1948 internship at St. Vincent Hospital, Portland. 1948-1951 Resident in dermatology, 1952-1956 Assistant Professor at the University of Chicago, Illinois. 1956-1967 Head, Division of Dermatology, 1958-1967 Associate Professor at the Western Reserve University. 1967-1977 Head, Division of Dermatology, at the Scripps Clinic and Research Foundation. 1974-1982 Director, Division of Dermatology, at the University of California, San Diego. Currently Professor of Medicine, Division of Dermatology, at the University Hospital, San Diego. Dr. Stoughton is Editor in Chief of the Journal of Investigative Dermatology, Member of Board of Directors of the American Academy of Dermatology, Member of Dermatology Advisory Board Food and Drug Administration, President of the Society for Investigative Dermatology, Member of American Board of Dermatology, and held many other offices. He has authored over 125 scientific publications.

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Potency Ranking of Some Commonly Used Topical Steroids

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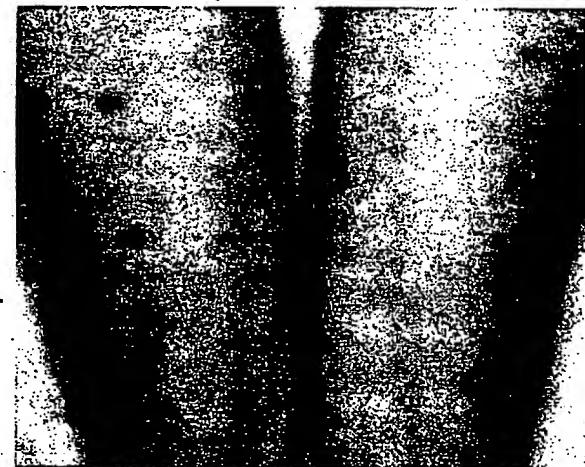
The most commonly used and accurate predictive method to assess the potency (clinical effectiveness) of a topical steroid is the vasoconstriction assay. Its results can then be correlated with those of a comparison study on diseased skin.

The vasoconstriction assay is easy to perform, permits simultaneous evaluation of a series of compounds, exposes the individual to only small amounts of the test material for a short period of time, and its results are reproducible.

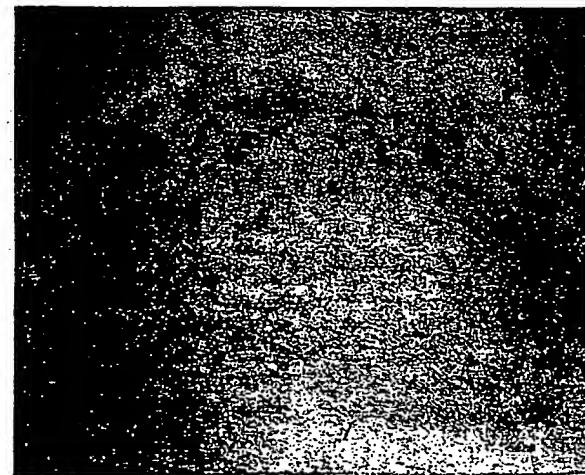
In the test the ability of various topical corticosteroids to cause blanching (vasoconstriction) is compared. Up to eight different formulations are applied to the flexural aspects of the forearms of normal volunteers. After application the test sites are covered with non-occlusive plastic guards. The degree of blanching is evaluated at the test sites 16 hours after application.

While the vasoconstriction assay provides a good first approximation of the activity of a steroid formulation, bilateral paired comparison studies on diseased skin offer a simple but direct assessment of clinical effectiveness. In these assays one compound is applied to a lesion on one side of the body and another one to an identical lesion on the opposite side of the body. Thus, two com-

pounds can be compared for clinical effectiveness on the same individual. Because the frequency of symmetrical involvement in psoriasis has often been used for such trials. Results from the vasoconstriction assay and clinical trials on diseased subjects correlate in virtually all instances. Using this correlation, one can categorize topical steroids into seven major potency groups.



Vasoconstriction test: Areas of severe vasoconstriction and areas of minimal - if any - vasoconstriction can be seen.



I.
Betamethasone dipropionate ointment 0.05%
(optimized vehicle)*

II.
Amcinonide ointment 0.1%
Betamethasone dipropionate ointment 0.05%
Desoximetasone cream 0.25%
Desoximetasone gel 0.05%
Desoximetasone ointment 0.25%
Diflorasone diacetate ointment 0.05%
Fluocinonide cream 0.05%
Fluocinonide gel 0.05%
Fluocinonide ointment 0.05%
Halcinonide cream 0.1%.

III.
Betamethasone dipropionate cream 0.05%
Betamethasone valerate ointment 0.1%
Diflorasone diacetate cream 0.05%
Triamcinolone acetonide cream 0.5%

IV.
Betamethasone benzoate ointment 0.025%
Desoximetasone cream 0.05%
Fluocinolone acetonide cream 0.2%
Fluocinolone acetonide ointment 0.025%
Flurandrenolide ointment 0.05%
Hydrocortisone valerate ointment 0.2%
Triamcinolone acetonide ointment 0.1%

V.
Betamethasone benzoate cream 0.025%
Betamethasone dipropionate lotion 0.02%
Betamethasone valerate cream 0.1%
Betamethasone valerate lotion 0.1%
Fluocinolone acetonide cream 0.025%
Flurandrenolide cream 0.05%
Hydrocortisone butyrate cream 0.1%
Hydrocortisone valerate cream 0.2%
Triamcinolone acetonide cream 0.1%
Triamcinolone acetonide lotion 0.1%

VI.
Desonide cream 0.05%
Fluocinolone acetonide solution 0.01%
Flumethasone pivalate cream 0.03%

VII.
Topicals with hydrocortisone, dexametasone, flumethalone, prednisolone and methylprednisolone

Group I is the most potent, and potency descends with each group to group VII, which is least potent (I,II,III = potent steroids, IV,V = mid-strength steroids, VI,VII = mild steroids). There is no significant difference between agents within any given group; within each group the compounds are arranged alphabetically.

This table is based on the experience of the authors in the U.S.A. We have not evaluated clobetasol propionate cream or ointment extensively enough to assign them to a specific category. Our preliminary data, however, indicate that clobetasol propionate is at least as potent as the group I steroids, and possibly even stronger.

** No more than 45 g per week should be applied.*

► *Comparison study: A potent steroid cream was compared to a mild steroid. Two lesions of psoriasis on the anterior thighs were selected. Medication was applied twice daily for 14 days. Both lesions were identical at onset of therapy. There was a significantly better response on the right side where the more potent agent was used.*

Appendix B

POTENCY RANKING OF SOME COMMONLY USED TOPICAL CORTICOSTEROIDS^{1,2*}

		Superhigh Potency	
TEMOVATE [®] Cream, 0.05% (clobetasol propionate)	I	TEMOVATE [®] Emollient Cream, 0.05%* (clobetasol propionate)	
TEMOVATE [®] Ointment, 0.05% (clobetasol propionate)		TEMOVATE [®] Gel, 0.05%* (clobetasol propionate)	
TEMOVATE Cream or Ointment is more potent than Diprolene Cream or Ointment and Psorcon Ointment		Diprolene [®] Cream, 0.05%	
Cyclocort [®] Ointment, 0.1% Diprolene [®] AF Cream, 0.05% Diprosone [®] Ointment, 0.05% Elocon [®] Ointment, 0.1% Florone [®] Ointment, 0.05% Halot [®] Cream, 0.1%	II	Lidex [®] Cream, 0.05% Lidex [®] Gel, 0.05% Lidex [®] Ointment, 0.05% Maxiflor [®] Ointment, 0.05% Topicort [®] Cream, 0.25% Topicort [®] Gel, 0.05% Topicort [®] Ointment, 0.25%	
Aristocort A [®] Ointment, 0.1% CUTIVATE [®] Ointment, 0.005%* (fluticasone propionate) Cyclocort [®] Cream, 0.1% Cyclocort [®] Lotion, 0.1% Diprosone [®] Cream, 0.05%	III	Florone [®] Cream, 0.05% Halot [®] Ointment, 0.1% Lidex-E [®] Cream, 0.05% Maxiflor [®] Cream, 0.05% Valisone [®] Ointment, 0.1%	
Cordran [®] Ointment, 0.05% Elocon [®] Cream, 0.1% Kenalog [®] Cream, 0.1%	IV	Synalar [®] Ointment, 0.025% Westcort [®] Ointment, 0.2%	
Cordran [®] Cream, 0.05% CUTIVATE [®] Cream, 0.05%* (fluticasone propionate) Diprosone [®] Lotion, 0.05% Kenalog [®] Lotion, 0.1%	V	Locoid [®] Cream, 0.1% Synalar [®] Cream, 0.025% Valisone [®] Cream, 0.1% Westcort [®] Cream, 0.2%	
ACLOVATE [®] Cream, 0.05% (aclometasone dipropionate) ACLOVATE [®] Ointment, 0.05% (aclometasone dipropionate) Aristocort [®] Cream, 0.1%	VI	Locorten [®] Cream, 0.03% Synalar [®] Cream, 0.01% Synalar [®] Solution, 0.01% Tridesilon [®] Cream, 0.05% Valisone [®] Lotion, 0.05%	
Topicals with dexamethasone, flumethalone, hydrocortisone,	VII	methylprednisolone, and prednisolone	

Adapted from Stoughton.¹

Class I is the superpotent category; potency descends with each class to class VII, which is least potent (II, III, potent steroids; IV, V, midstrength steroids; VI, VII, mild steroids). There is no significant difference between agents within classes II through VII; the compounds are simply arranged alphabetically. However, within class I, TEMOVATE Cream or Ointment is more potent than Diprolene Cream or Ointment and Psorcon Ointment.

Use of superhigh-potency topical corticosteroids in children under 12 years of age is not recommended.
Classification of TEMOVATE E, TEMOVATE Gel, CUTIVATE Cream, and CUTIVATE Ointment in this potency ranking chart per written communication from the laboratory of RB Stoughton, MD and DJ Piacquadio, MD.

Reference: 1. Stoughton RB. Vasoconstrictor assay—specific applications. In: Maibach HI, Surber C, eds. *Topical Corticosteroids*. Basel, Switzerland: Karger; 1992:42-53.
Please see accompanying complete Prescribing Information.

Appendix C

Serevent—Cont.

Respiratory			
Cough	6	7	3
Lower respiratory infection	2	4	2

*The only adverse experience classified as serious was one case of upper respiratory tract infection in a patient treated with albuterol.

The table above includes all events (whether considered drug related or non-drug related by the investigator) that occurred at a rate of over 3% in the SEREVENT Inhalation Aerosol treatment group and were more common in the SEREVENT Inhalation Aerosol group than in the placebo group.

Pharyngitis, allergic rhinitis, dizziness/giddiness, and influenza occurred at 3% or more but were equally common on placebo. Other events occurring in the SEREVENT Inhalation Aerosol treatment group at a frequency of 1% to 3% were as follows:

Cardiovascular: Tachycardia, palpitations.

Ear, Nose, and Throat: Rhinitis, laryngitis.

Gastrointestinal: Nausea, viral gastroenteritis, nausea and vomiting, diarrhea, abdominal pain.

Hypersensitivity: Urticaria.

Mouth and Teeth: Dental pain.

Musculoskeletal: Pain in joint, back pain, muscle cramp/contraction, myalgia/myositis, muscular soreness.

Neurological: Nervousness, malaise/fatigue.

Respiratory: Tracheitis/tracheitis.

Skin: Rash/skin eruption.

Urogenital: Dysmenorrhea.

In small dose-response studies, tremor, nervousness, and palpitations appeared to be dose related.

Postmarketing Experience: In extensive US and worldwide postmarketing experience, serious exacerbations of asthma, including some that have been fatal, have been reported. In most cases, these have occurred in patients with severe asthma and/or in some patients in whom asthma has been acutely deteriorating (see **WARNINGS** no. 1), but they have occurred in a few patients with less severe asthma as well. It was not possible from these reports to determine whether SEREVENT Inhalation Aerosol contributed to these events or simply failed to relieve the deteriorating asthma.

Postmarketing experience includes rare reports of upper airway symptoms of laryngeal spasm, irritation, or swelling, such as stridor and choking. Hypertension and arrhythmias have been reported.

OVERDOSAGE

Overdose with salmeterol may be expected to result in exaggeration of the pharmacologic adverse effects associated with beta-adrenoceptor agonists, including tachycardia and/or arrhythmia, tremor, headache, and muscle cramps. Overdose with salmeterol can lead to clinically significant prolongation of the QTc interval, which can produce ventricular arrhythmias. Other signs of overdose may include hypokalemia and hyperglycemia.

In these cases, therapy with SEREVENT Inhalation Aerosol and all beta-adrenergic stimulant drugs should be stopped, supportive therapy provided, and judicious use of a beta-adrenergic blocking agent should be considered, bearing in mind the possibility that such agents can produce bronchospasm. Cardiac monitoring is recommended in cases of overdose.

As with all sympathomimetic pressurized aerosol medications, cardiac arrest and even death may be associated with abuse of SEREVENT Inhalation Aerosol.

Rats and dogs survived the maximum practicable inhalation doses of salmeterol of 2.9 and 0.7 mg/kg, respectively. The maximum nonlethal oral doses in mice and rats were approximately 150 mg/kg and >1,000 mg/kg, respectively. Dialysis is not appropriate treatment for overdosage of SEREVENT Inhalation Aerosol.

DOSAGE AND ADMINISTRATION

SEREVENT Inhalation Aerosol should be administered by the orally inhaled route only (see **Patient's Instructions for Use**). For maintenance of bronchodilation and prevention of symptoms of asthma, including the symptoms of nocturnal asthma, the usual dosage for adults and children 12 years of age and older is two inhalations (42 mcg) twice daily (morning and evening, approximately 12 hours apart). Adverse effects are more likely to occur with higher doses of salmeterol, and more frequent administration or administration of a larger number of inhalations is not recommended.

To gain full therapeutic benefit, SEREVENT Inhalation Aerosol should be administered twice daily (morning and evening) in the treatment of reversible airway obstruction. If a previously effective dosage regimen fails to provide the usual response, medical advice should be sought immediately as this is often a sign of destabilization of asthma. Un-

der these circumstances, the therapeutic regimen should be reevaluated and additional therapeutic options, such as inhaled or systemic corticosteroids, should be considered. If symptoms arise in the period between doses, a short-acting inhaled beta-agonist should be taken for immediate relief. **Prevention of Exercise-Induced Bronchospasm:** Two inhalations at least 30 to 60 minutes before exercise have been shown to protect against exercise-induced bronchospasm in many patients for up to 12 hours. Additional doses of SEREVENT Inhalation Aerosol should not be used for 12 hours after the administration of this drug. Patients who are receiving SEREVENT Inhalation Aerosol twice daily (morning and evening) should not use additional SEREVENT Inhalation Aerosol for prevention of exercise-induced bronchospasm. If this dose is not effective, other appropriate therapy for exercise-induced bronchospasm should be considered.

Geriatric Use: In studies where geriatric patients (65 years of age or older, see **PRECAUTIONS**) have been treated with SEREVENT Inhalation Aerosol, efficacy and safety of 42 mcg given twice daily (morning and evening) did not differ from that in younger patients. Consequently, no dosage adjustment is recommended.

HOW SUPPLIED

SEREVENT Inhalation Aerosol is supplied in 18-g canisters containing 120 metered actuations in boxes of one. Each actuation delivers 25 mcg of salmeterol base (as salmeterol xinafoate) from the valve and 21 mcg of salmeterol base (as salmeterol xinafoate) from the actuator. Each canister is supplied with a green plastic actuator with a teal-colored strapcap and patient's instructions (NDC 0173-0464-00). Also available, SEREVENT Inhalation Aerosol Refill (NDC 0173-0465-00), a 18-g canister only with patient's instructions.

SEREVENT Inhalation Aerosol is also supplied in a pack that consists of a 6.5-g canister containing 60 metered actuations in boxes of one. Each actuation delivers 25 mcg of salmeterol base (as salmeterol xinafoate) from the valve and 21 mcg of salmeterol base from the actuator (as salmeterol xinafoate). Each canister is supplied with a green plastic actuator with a teal-colored strapcap and patient's instructions (NDC 0173-0467-00).

For use with SEREVENT Inhalation Aerosol actuator only. The actuator should not be used with other aerosol medications.

Store between 15° and 30°C (59° and 86°F). Store canister with nozzle end down. Protect from freezing temperatures and direct sunlight.

Avoid spraying in eyes. Contents under pressure. Do not puncture or incinerate. Do not store at temperatures above 120°F. Keep out of reach of children. As with most inhaled medications in aerosol canisters, the therapeutic effect of this medication may decrease when the canister is cold; for best results, the canister should be at room temperature before use. Shake well before using.

September 1996/RL-352

Shown in *Product Identification Guide*, page 319

TEMOVATE®

[tim'-ö-vät*]
(clobetasol propionate cream)

Cream, 0.05%.

TEMOVATE®
(clobetasol propionate ointment)
Ointment, 0.05%.

For Dermatologic Use Only—
Not for Ophthalmic Use.

DESCRIPTION

TEMOVATE (clobetasol propionate cream and ointment) Cream and Ointment contain the active compound clobetasol propionate, a synthetic corticosteroid, for topical dermatologic use. Clobetasol, an analog of prednisolone, has a high degree of glucocorticoid activity and a slight degree of mineralocorticoid activity.

Chemically, clobetasol propionate is (118,168)-21-chloro-9-fluoro-11-hydroxy-16-methyl-17-(1-oxopropoxy)-pregna-1,4-diene-3,20-dione.

Clobetasol propionate has the empirical formula $C_{28}H_{32}ClFO_5$ and a molecular weight of 467. It is a white to cream-colored crystalline powder insoluble in water. TEMOVATE Cream contains clobetasol propionate 0.5 mg/g in a cream base of propylene glycol, glyceryl monostearate, cetylstearyl alcohol, glyceryl stearate, PEG 100 stearate, white wax, chlorocresol, sodium citrate, citric acid monohydrate, and purified water.

TEMOVATE Ointment contains clobetasol propionate 0.5 mg/g in a base of propylene glycol, sorbitan sesquioleate, and white petrolatum.

CLINICAL PHARMACOLOGY

Like other topical corticosteroids, clobetasol propionate has anti-inflammatory, antipruritic, and vasoconstrictive prop-

erties. The mechanism of the anti-inflammatory activity of the topical steroids, in general, is unclear. However, corticosteroids are thought to act by the induction of phosphoprotein A₂, inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor, arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A₂.

Pharmacokinetics: The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the vehicle and the integrity of the epidermal barrier. Occlusive dressing with hydrocortisone for up to 24 hours has not been demonstrated to increase penetration; however, occlusion of hydrocortisone for 96 hours markedly enhances penetration. Topical corticosteroids can be absorbed from normal, intact skin. Inflammation and/or other disease processes in the skin may increase percutaneous absorption.

Studies performed with TEMOVATE Cream and Ointment indicate that they are in the super-high range of potency compared with other topical corticosteroids.

INDICATIONS AND USAGE

TEMOVATE Cream and Ointment are super-high potency corticosteroid formulations indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. Treatment beyond 2 consecutive weeks is not recommended, and the total dosage should not exceed 50 g/week because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis. Use in children under 12 years of age is not recommended. As with other highly active corticosteroids, therapy should be discontinued when control has been achieved. If no improvement is seen within 2 weeks, reassessment of the dosage may be necessary.

CONTRAINDICATIONS

TEMOVATE Cream and Ointment are contraindicated in those patients with a history of hypersensitivity to any of the components of the preparations.

PRECAUTIONS

General: TEMOVATE Cream and Ointment should not be used in the treatment of rosacea or periorificial dermatitis, and should not be used on the face, groin, or axillas.

Systemic absorption of topical corticosteroids can produce reversible HPA axis suppression with the potential for glucocorticoid insufficiency after withdrawal from treatment. Manifestations of Cushing's syndrome, hyperglycemia, and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on therapy.

Patients applying a topical steroid to a large surface area or to areas under occlusion should be evaluated periodically for evidence of HPA axis suppression. This may be done by using the ACTH stimulation, A.M. plasma cortisol, and urinary free cortisol tests. Patients receiving super-potent corticosteroids should not be treated for more than 2 weeks at a time, and only small areas should be treated at any one time due to the increased risk of HPA suppression.

TEMOVATE Cream and Ointment produced HPA axis suppression when used at doses as low as 2 g/day for 1 week in patients with eczema.

If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent corticosteroid. Recovery of HPA axis function is generally prompt upon discontinuation of topical corticosteroids. Infrequently, signs and symptoms of glucocorticoid insufficiency may occur, requiring supplemental systemic corticosteroids. For information on systemic supplementation, see prescribing information for those products.

Pediatric patients may be more susceptible to systemic toxicity from equivalent doses due to their larger skin surface to body mass ratio (see **PRECAUTIONS: Pediatric Use**). If irritation develops, TEMOVATE Cream and Ointment should be discontinued and appropriate therapy instituted. Allergic contact dermatitis with corticosteroids is usually diagnosed by observing failure to heal rather than noting a clinical exacerbation as with most topical products not containing corticosteroids. Such an observation should be corroborated with appropriate diagnostic patch testing.

If concomitant skin infections are present or develop, an appropriate antifungal or antibacterial agent should be used. If a favorable response does not occur promptly, use of TEMOVATE Cream and Ointment should be discontinued until the infection has been adequately controlled.

Information for Patients: Patients using topical corticosteroids should receive the following information and instructions:

1. This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.
2. This medication should not be used for any disorder other than that for which it was prescribed.

PRODUCT INFORMATION

3. The treated skin area should not be bandaged, otherwise covered, or wrapped so as to be occlusive unless directed by the physician.

4. Patients should report any signs of local adverse reactions to the physician.

Laboratory Tests: The following tests may be helpful in evaluating patients for HPA axis suppression:

ACTH stimulation test

A.M. plasma cortisol test

Urinary free cortisol test

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term animal studies have not been performed to evaluate the carcinogenic potential of clobetasol propionate.

Studies in the rat following oral administration at dosage levels up to 50 mg/kg per day revealed that the females exhibited an increase in the number of resorbed embryos and a decrease in the number of living fetuses at the highest dose.

Clobetasol propionate was nonmutagenic in three different test systems: the Ames test, the *Saccharomyces cerevisiae* gene conversion assay, and the *E. coli* B WP2 fluctuation test.

Pregnancy: Teratogenic Effects: Pregnancy Category C: Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application to laboratory animals.

Clobetasol propionate has not been tested for teratogenicity when applied topically; however, it is absorbed percutaneously, and when administered subcutaneously it was a significant teratogen in both the rabbit and mouse. Clobetasol propionate has greater teratogenic potential than steroids that are less potent.

Teratogenicity studies in mice using the subcutaneous route resulted in fetotoxicity at the highest dose tested (1 mg/kg) and teratogenicity at all dose levels tested down to 0.03 mg/kg. These doses are approximately 0.33 and 0.01 times, respectively, the human topical dose of TEMOVATE Cream and Ointment. Abnormalities seen in TEMOVATE Cream and Ointment. Abnormalities seen included cleft palate and skeletal abnormalities.

In rabbits, clobetasol propionate was teratogenic at doses of 1 and 10 mcg/kg. These doses are approximately 0.001 and 0.03 times, respectively, the human topical dose of TEMOVATE Cream and Ointment. Abnormalities seen included cleft palate, cranioschisis, and other skeletal abnormalities.

There are no adequate and well-controlled studies of the teratogenic potential of clobetasol propionate in pregnant women. TEMOVATE Cream and Ointment should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when TEMOVATE Cream or Ointment is administered to a nursing woman.

External Use: Safety and effectiveness of TEMOVATE in pediatric patients have not been established. Use in children under 12 years of age is not recommended. Because of the ratio of skin surface area to body mass, pediatric patients are at a greater risk than adults of HPA axis suppression and Cushing's syndrome when they are treated with topical corticosteroids. They are therefore also at greater risk of adrenal insufficiency during or after withdrawal of treatment. Adverse effects including striae have been reported with inappropriate use of topical corticosteroids in infants and children.

Adrenal Suppression: Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include low plasma cortisol levels and an absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and papilledema.

Local Reactions: In controlled clinical trials, the most frequent adverse reactions reported for TEMOVATE Cream, were burning and stinging in 1% of treated patients. Less frequent adverse reactions were itching, skin atrophy, and cracking scaling of the skin.

In controlled clinical trials, the most frequent adverse reactions reported for TEMOVATE Ointment were burning and stinging, and itching in 0.5% of treated patients. Less frequent adverse reactions were stinging, cracking, erosion, edema, numbness of fingers, skin atrophy, and cracking scaling of the skin.

Cushing's syndrome has been reported in infants and adults with prolonged use of topical clobetasol propionate.

The following additional local adverse reactions have been reported with topical corticosteroids, and they may occur more frequently with the use of occlusive dressings and higher potency corticosteroids. These reactions are listed in an approximately decreasing order of occurrence: dryness, acneiform eruptions, hypopigmentation, periorificial dermatitis, allergic contact dermatitis, secondary infection, irritation, striae, and milia.

OVERDOSAGE

Typically applied TEMOVATE Cream and Ointment can be absorbed in sufficient amounts to produce systemic effects (see PRECAUTIONS).

DOSAGE AND ADMINISTRATION

Apply a thin layer of TEMOVATE Cream or Ointment to the affected skin areas twice daily and rub in gently and completely.

TEMOVATE Cream and Ointment are super-high potency topical corticosteroids; therefore, treatment should be limited to 2 consecutive weeks, and amounts greater than 50 g/week should not be used.

As with other highly active corticosteroids, therapy should be discontinued when control has been achieved. If no improvement is seen within 2 weeks, reassessment of diagnosis may be necessary.

TEMOVATE Cream and Ointment should not be used with occlusive dressings.

HOW SUPPLIED

TEMOVATE Cream, 0.05% is supplied in 15-g (NDC 0173-0375-73), 30-g (NDC 0173-0375-72), 45-g (NDC 0173-0375-01), and 60-g (NDC 0173-0375-02) tubes.

TEMOVATE Ointment, 0.05% is supplied in 15-g (NDC 0173-0376-73), 30-g (NDC 0173-0376-72), 45-g (NDC 0173-0376-01), and 60-g (NDC 0173-0376-02) tubes.

Store between 15° and 30°C (59° and 86°F). TEMOVATE Cream should not be refrigerated.

September 1996/RU-356

Shown in Product Identification Guide, page 313

TEMOVATE®

(tim' vāt')

(clobetasol propionate gel)

gel, 0.05%

**FOR TOPICAL DERMATOLOGIC USE ONLY—
NOT FOR OPHTHALMIC, ORAL, OR INTRAVAGINAL
USE**

DESCRIPTION

TEMOVATE Gel contains the active compound clobetasol propionate, a synthetic corticosteroid, for topical dermatologic use. Clobetasol, an analog of prednisolone, has a high degree of glucocorticoid activity and a slight degree of mineralocorticoid activity.

Chemically, clobetasol propionate is (11 β ,16 β)-21-chloro-9-fluoro-11-hydroxy-16-methyl-17-(1-oxopropoxy)-pregna-1,4-diene-3,20-dione.

Clobetasol propionate has the empirical formula $C_{25}H_{28}ClFO_4$ and a molecular weight of 467. It is a white to cream-colored crystalline powder insoluble in water.

TEMOVATE Gel contains clobetasol propionate 0.5 mg/g in a base of propylene glycol, carbomer 934P, sodium hydroxide, and purified water.

CLINICAL PHARMACOLOGY

Like other topical corticosteroids, clobetasol propionate has anti-inflammatory, antipruritic, and vasoconstrictive properties. The mechanism of the anti-inflammatory activity of the topical steroids, in general, is unclear. However, corticosteroids are thought to act by the induction of phospholipase A₂ inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor, arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A₂.

Pharmacokinetics: The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the vehicle and the integrity of the epidermal barrier. Occlusive dressing with hydrocortisone for up to 24 hours has not been demonstrated to increase penetration; however, occlusion of hydrocortisone for 96 hours markedly enhances penetration. Topical corticosteroids can be absorbed from normal intact skin, while inflammation and/or other disease processes in the skin may increase percutaneous absorption. Greater absorption was observed for the TEMOVATE gel formulation as compared to the cream formulation in *in vitro* human skin penetration studies.

Studies performed with TEMOVATE Gel indicate that it is in the super-high range of potency as compared with other topical corticosteroids.

INDICATIONS AND USAGE.

TEMOVATE Gel is a super-high potency corticosteroid formulation indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. Treatment beyond 2 consecutive weeks is not recommended, and the total dosage should not exceed 50 g/week because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis. Use in children under 12 years of age is not recommended.

CONTRAINDICATIONS

TEMOVATE Gel is contraindicated in those patients with history of hypersensitivity to any of the components of the preparation.

PRECAUTIONS

General: Clobetasol propionate is a highly potent topical corticosteroid that has been shown to suppress the HPA axis at doses as low as 2 g/day.

Systemic absorption of topical corticosteroids can produce reversible HPA axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal from treatment. Manifestations of Cushing's syndrome, hyperglycemia, and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on therapy.

Patients receiving a large dose applied to a large surface area should be evaluated periodically for evidence of HPA axis suppression. This may be done by using the ACTH stimulation, A.M. plasma cortisol, and urinary free cortisol tests. Patients receiving super-potent corticosteroids should not be treated for more than 2 weeks at a time, and only small areas should be treated at any one time due to the increased risk of HPA suppression.

If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent corticosteroid. Recovery of HPA axis function is generally prompt and complete upon discontinuation of topical corticosteroids. Infrequently, signs and symptoms of glucocorticoid insufficiency may occur that require supplemental systemic corticosteroids. For information on systemic supplementation, see prescribing information for those products.

Children may be more susceptible to systemic toxicity from equivalent doses due to their larger skin surface to body mass ratio (see PRECAUTIONS: Pediatric Use).

If irritation develops, TEMOVATE Gel should be discontinued and appropriate therapy instituted. Allergic contact dermatitis with corticosteroids is usually diagnosed by observing failure to heal rather than noting a clinical exacerbation as with most topical products not containing corticosteroids. Such an observation should be corroborated with appropriate diagnostic patch testing.

If concomitant skin infections are present or develop, an appropriate antifungal or antibacterial agent should be used. If a favorable response does not occur promptly, use of TEMOVATE Gel should be discontinued until the infection has been adequately controlled.

TEMOVATE Gel should not be used in the treatment of rosacea or periorificial dermatitis, and should not be used on the face, groin, or axilla.

Information for Patients: Patients using topical corticosteroids should receive the following information and instructions:

1. This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.
2. This medication should not be used for any disorder other than that for which it was prescribed.
3. The treated skin area should not be bandaged or otherwise covered or wrapped so as to be occlusive unless directed by the physician.
4. Patients should report any signs of local adverse reactions to the physician.
5. Patients should inform their physicians that they are using TEMOVATE if surgery is contemplated.

Laboratory Tests: The following tests may be helpful in evaluating patients for HPA axis suppression: ACTH stimulation test, A.M. plasma cortisol test, Urinary free cortisol test.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term animal studies have not been performed to evaluate the carcinogenic potential of clobetasol propionate.

Studies in the rat following oral administration at dosage levels up to 50 mg/kg per day revealed no significant effect on the males. The females exhibited an increase in the number of resorbed embryos and a decrease in the number of living fetuses at the highest dose.

Clobetasol propionate was nonmutagenic in three different test systems: the Ames test, the *Saccharomyces cerevisiae* gene conversion assay, and the *E. coli* B WP2 fluctuation test.

Pregnancy: Teratogenic Effects: Pregnancy Category C: Corticosteroids have been shown to be teratogenic in laboratory animals.

Continued on next page

PRODUCT INFORMATION

NDC 0173-0414-00 1-g* Vial (Tray of 25)
 NDC 0173-0415-00 2-g* Vial (Tray of 25)
 NDC 0173-0416-00 1-g* Infusion Pack (Tray of 10)
 NDC 0173-0417-00 2-g* Infusion Pack (Tray of 10)
 NDC 0173-0418-00 10-g* Pharmacy Bulk Package (Tray of 5)

*Equivalent to amiodarone ceftazidime.

REFERENCES

1. Bauer AW, Kirby WMM, Sherris JC, Turk M. Antibiotic susceptibility testing by a standardized single disk method. *Am J Clin Pathol*. 1966;45:493-495.
2. National Committee for Clinical Laboratory Standards. *Approved Standard: Performance Standards for Antimicrobial Disk Susceptibility Tests (M2-A3)*. December 1984.
3. Certification procedure for antibiotic sensitivity discs (21 CFR 480.1). *Federal Register*. May 30, 1974;39:19182-19184.
4. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16:31-41.

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 VIAFLEX and PL 146 Plastic are registered trademarks of Baxter International Inc.
 U.S. Patents 4,258,041; 4,329,453; and 4,582,830
 September 1996/RL-372

Shown in Product Identification Guide, page 311

CUTIVATE®

[kyoot' s-oo-tiv']

(fluticasone propionate cream)

Cream, 0.05%

For Dermatologic Use Only—
 Not for Ophthalmic Use.

DESCRIPTION

CUTIVATE Cream contains fluticasone propionate [(6a, 9a, 16a, 17a)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-(1-exopropoxy)androsta-1,4-diene-17-carbothioic acid, 2-fluoromethyl ester], a synthetic fluorinated corticosteroid, for topical dermatologic use. The topical corticosteroids constitute a class of primarily synthetic steroids used as anti-inflammatory and antipruritic agents.

Chemically, fluticasone propionate is $C_{21}H_{21}F_3O_5S$.

Fluticasone propionate has a molecular weight of 500.6. It is a white to off-white powder and is insoluble in water.

Each gram of CUTIVATE Cream contains fluticasone propionate 0.5 mg in a base of propylene glycol, mineral oil, cetearyl alcohol, Ceteth-20, isopropyl myristate, dibasic sodium phosphate, citric acid, purified water, and imidurea as preservative.

CLINICAL PHARMACOLOGY

Like other topical corticosteroids, fluticasone propionate has anti-inflammatory, antipruritic, and vasoconstrictive properties. The mechanism of the anti-inflammatory activity of the topical steroids, in general, is unclear. However, corticosteroids are thought to act by the induction of phospholipase A_2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor, arachidonic acid. Arachidonic acid is released from the membrane phospholipids by phospholipase A_2 .

Fluticasone propionate is lipophilic and has a strong affinity for the glucocorticoid receptor. It has weak affinity for the progesterone receptor, and virtually no affinity for the mineralocorticoid, estrogen, or androgen receptors. The therapeutic potency of glucocorticoids is related to the half-life of the glucocorticoid-receptor complex. Fluticasone propionate binding to the glucocorticoid receptor is rapid. The half-life of the fluticasone propionate-glucocorticoid receptor complex is approximately 10 hours.

Pharmacokinetics: The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the vehicle and the integrity of the epidermal barrier. Occlusive dressing enhances penetration. Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption. Fluticasone propionate absorbed systemically is rapidly metabolized in the liver by esterases, primarily hydrolysis to the 17- β -carboxylic acid, which has minimal glucocorticoid or anti-inflammatory activity. Studies performed with CUTIVATE Cream indicate that it has a medium range of potency as compared with other topical corticosteroids.

INDICATIONS AND USAGE

CUTIVATE Cream is a medium potency corticosteroid indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

CONTRAINDICATIONS

CUTIVATE Cream is contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

PRECAUTIONS

General: Systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal from treatment. Manifestations of Cushing's syndrome, hyperglycemia, and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on treatment.

Patients applying a potent topical steroid to a large surface area or to areas under occlusion should be evaluated periodically for evidence of HPA axis suppression. This may be done by using the ACTH stimulation, A.M. plasma cortisol, and urinary free cortisol tests.

Fluticasone propionate cream, 0.05% caused depression of A.M. plasma cortisol levels in one of six patients when used daily for 7 days in patients with psoriasis or eczema involving at least 30% of the body surface. After 2 days of treatment, this patient developed a 60% decrease from pretreatment values in the A.M. plasma cortisol level. There was some evidence of corresponding decrease in the 24-hour urinary free cortisol levels. The A.M. plasma cortisol level remained slightly depressed for 48 hours before recovering by day 6 of treatment.

If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid. Recovery of HPA axis function is generally prompt upon discontinuation of topical corticosteroids. Infrequently, signs and symptoms of glucocorticosteroid insufficiency may occur requiring systemic corticosteroids. For information on systemic supplementation, see prescribing information for those products. Children may be more susceptible to systemic toxicity from equivalent doses due to their larger skin surface to body mass ratios (see PRECAUTIONS: Pediatric Use).

If irritation develops, CUTIVATE Cream should be discontinued and appropriate therapy instituted. Allergic contact dermatitis with corticosteroids is usually diagnosed by observing failure to heal rather than noting a clinical exacerbation as with most topical products not containing corticosteroids. Such an observation should be corroborated with appropriate patch testing.

If concomitant skin infections are present or develop, an appropriate antifungal or antibacterial agent should be used. If a favorable response does not occur promptly, use of CUTIVATE Cream should be discontinued until the infection has been adequately controlled.

CUTIVATE Cream should not be used in the treatment of preexisting skin atrophy and should not be used where infection is present at the treatment site. CUTIVATE Cream should not be used in the treatment of rosacea and perioral dermatitis.

Information for Patients: Patients using topical corticosteroids should receive the following information and instructions:

1. This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.
2. This medication should not be used for any disorder other than that for which it was prescribed.
3. The treated skin area should not be bandaged or otherwise covered or wrapped so as to be occlusive unless directed by the physician.
4. Patients should report to their physician any signs of local adverse reactions.

Laboratory Tests: The following tests may be helpful in evaluating patients for HPA axis suppression:

ACTH stimulation test

A.M. plasma cortisol test

Urinary free cortisol test

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Two 18-month studies were performed in mice to evaluate the carcinogenic potential of fluticasone propionate when given topically (as an 0.05% ointment) and orally. No evidence of carcinogenicity was found in either study.

Fluticasone propionate was not mutagenic in the standard Ames test, *E. coli* fluctuation test, *S. cerevisiae* gene conversion test, or Chinese Hamster ovarian cell assay. It was not clastogenic in mouse micronucleus or cultured human lymphocyte tests.

In a fertility and general reproductive performance study in rats, fluticasone propionate administered subcutaneously to females at up to 50 mg/kg per day and to males up to 100 mg/kg per day (later reduced to 50 mg/kg per day) had no effect upon mating performance or fertility. These doses are approximately 15 and 30 times, respectively, the human systemic exposure following use of the recommended human topical dose of fluticasone propionate cream, 0.05%, assuming human percutaneous absorption of approximately 3% and the use in a 70-kg person of 15 g/day.

Pregnancy: Teratogenic Effects: Pregnancy Category C: Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. Teratology studies in the mouse demonstrated fluticasone propionate to be teratogenic (cleft palate) when administered subcutaneously in doses of 45 mg/kg per day and 150 mg/kg per day. This dose is approximately 14 and 45 times, respectively, the human topical dose of fluticasone propionate cream, 0.05%. There are no adequate and well-controlled studies in pregnant women. CUTIVATE Cream should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when CUTIVATE Cream is administered to a nursing woman.

Pediatric Use: Safety and Effectiveness in pediatric patients have not been established. Because of a higher ratio of skin surface area to body mass, pediatric patients are at a greater risk than adults of HPA axis suppression when they are treated with topical corticosteroids. They are therefore also at greater risk of glucocorticosteroid insufficiency after withdrawal of treatment and of Cushing's syndrome while on treatment. Adverse effects including striae have been reported with inappropriate use of topical corticosteroids in infants and children.

HPA axis suppression, Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include low plasma cortisol levels and an absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

ADVERSE REACTIONS

In controlled clinical trials on b.i.d. administration, the total incidence of adverse reactions associated with the use of CUTIVATE Cream was approximately 4%. These adverse reactions were usually mild, self-limiting, and consisted primarily of pruritus, dryness, numbness of fingers, and burning. These events occurred in 2.9%, 1.2%, 1.0%, and 0.6% of patients, respectively.

The following additional local adverse reactions have been reported infrequently with topical corticosteroids (including fluticasone propionate), and they may occur more frequently with the use of occlusive dressings and higher potency corticosteroids. These reactions are listed in an approximately decreasing order of occurrence: irritation, folliculitis, acneiform eruptions, hypopigmentation, periorificial dermatitis, allergic contact dermatitis, secondary infection, skin atrophy, striae, and milia. Also, there are reports of the development of psudotumidus psoriasis from chronic plaque psoriasis following reduction or discontinuation of potent topical corticosteroid products.

In a clinical study that compared q.d. and b.i.d. administration of CUTIVATE Cream, the local adverse events that were considered to be drug related were as follows.

Table 1: Drug-Related Adverse Events—Skin

Adverse Events	Fluticasone q.d.	Fluticasone b.i.d.
Skin infection	1 (0.8%)	0
Infected eczema	1 (0.8%)	2 (1.6%)
Viral warts	0	1 (0.8%)
Herpes simplex	0	1 (0.8%)
Impetigo	1 (0.8%)	0
Atopic dermatitis	1 (0.8%)	0
Eczema	1 (0.8%)	0
Exacerbation of eczema	4 (3.0%)	1 (0.8%)
Erythema	0	2 (1.6%)
Burning	0	2 (1.6%)
Stinging	0	1 (0.8%)
Skin irritation	6 (4.5%)	3 (2.3%)
Puritus	2 (1.5%)	4 (3.0%)
Exacerbation of pruritus	1 (0.8%)	1 (0.8%)
Folliculitis	0	1 (0.8%)
Blisters	0	1 (0.8%)
Dryness of skin	1 (0.8%)	1 (0.8%)

OVERDOSAGE

Topically applied CUTIVATE Cream can be absorbed in sufficient amounts to produce systemic effects (see PRECAUTIONS).

Continued on next page

Consult 1998 PDR® supplements and future editions for revisions.

1016/GLAXO WELLCOME INC.

PHYSICIANS' DESK REFERENCE

Cutivate Cream—Cont.**DOSAGE AND ADMINISTRATION**

Eczema: Apply a thin film of CUTIVATE Cream to the affected skin areas once or twice daily. Rub in gently.

Other Corticosteroid-Responsive Dermatoses: Apply a thin film of CUTIVATE Cream to the affected skin areas twice daily. Rub in gently.

As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 2 weeks, reassessment of diagnosis may be necessary.

CUTIVATE Cream should not be used with occlusive dressings.

HOW SUPPLIED

CUTIVATE Cream is supplied in 15-g (NDC 0173-0430-00), 30-g (NDC 0173-0430-01) and 60-g (NDC 0173-0430-02) tubes.

Store between 2° and 30°C (36° and 86°F).

CLINICAL STUDIES

Psoriasis Studies: In two vehicle-controlled studies, CUTIVATE Cream applied twice daily was significantly more effective than the vehicle in the treatment of moderate to severe psoriasis. The investigator's global evaluation after 28 days of treatment is shown in the following table:

Table 2: Physician's Assessment of Clinical Response

	CUTIVATE Cream		Vehicle	
	Study 1 (n = 59)	Study 2 (n = 74)	Study 1 (n = 66)	Study 2 (n = 76)
Cleared	8%	1%	3%	1%
Excellent	29%	28%	11%	17%
Good	27%	34%	20%	28%
Fair	27%	15%	33%	25%
Poor	7%	22%	24%	27%
Worse	2%	0%	9%	1%

The clinical signs of psoriasis were scored on a scale of 0 = absent, 1 = mild, 2 = moderate, and 3 = severe. The mean improvement in the clinical signs at the end of treatment are shown in the following table:

Table 3: Signs and Symptoms: Mean Improvement Over Baseline

	CUTIVATE Cream		Vehicle	
	Study 1	Study 2	Study 1	Study 2
Erythema	1.19	1.07	0.55	0.64
Thickening	1.22	1.17	0.81	0.97
Scaling	1.53	1.39	0.96	1.21

Eczema Studies: In two controlled 28-day studies, CUTIVATE Cream q.d. was equivalent to CUTIVATE Cream b.i.d. in the treatment of moderate to severe eczema. The investigator's global evaluation after 28 days of treatment is shown in the following table:

Table 4: Physician's Assessment of Clinical Response

	CUTIVATE Cream q.d.		CUTIVATE Cream b.i.d.	
	Study 1 (n = 64)	Study 2 (n = 106)	Study 1 (n = 65)	Study 2 (n = 100)
Cleared	30%	20%	48%	21%
Excellent	42%	32%	32%	50%
Good	17%	26%	5%	12%
Fair	3%	14%	6%	10%
Poor	5%	3%	8%	6%
Worse	3%	6%	2%	3%

The clinical signs of eczema were scored on a scale of 0 = absent, 1 = mild, 2 = moderate, and 3 = severe. The mean improvement in the clinical signs at the end of treatment are shown in the following table:

Table 5: Signs and Symptoms: Mean Improvement Over Baseline

	CUTIVATE Cream q.d.		CUTIVATE Cream b.i.d.	
	Study 1	Study 2	Study 1	Study 2
Erythema	1.7	1.5	1.8	1.7
Puritus	2.1	1.6	2.1	1.7
Thickening	1.6	1.3	1.6	1.5
Lichenification	1.2	1.2	1.2	1.3
Vesiculation	0.5	0.4	0.5	0.5
Crusting	0.6	0.7	0.8	0.8

Caution: Federal (U.S.A.) law prohibits dispensing without prescription.

April 1997/RL-422

Shown in Product Identification Guide, page 311

CUTIVATE®

[kyoo'-tuh-vayt']

(fluticasone propionate ointment)

Ointment, 0.005%

For Dermatologic Use Only—

Not for Ophthalmic Use.

quiring supplemental systemic corticosteroids. For information on systemic supplementation, see prescribing information for those products.

Children may be more susceptible to systemic toxicity from equivalent doses due to their larger skin surface to body mass ratios (see PRECAUTIONS: Pediatric Use).

If irritation develops, CUTIVATE Ointment should be discontinued and appropriate therapy instituted. Allergic contact dermatitis with corticosteroids is usually diagnosed by observing failure to heal rather than noting a clinical exacerbation as with most topical products not containing corticosteroids. Such an observation should be corroborated with appropriate diagnostic patch testing.

If concomitant skin infections are present or develop, an appropriate antifungal or antibacterial agent should be used. If a favorable response does not occur promptly, use of CUTIVATE Ointment should be discontinued until the infection has been adequately controlled.

CUTIVATE Ointment should not be used in the treatment of preexisting skin atrophy and should not be used where infection is present at the treatment site. CUTIVATE Ointment should not be used in the treatment of rosacea and periorificial dermatitis.

Information for Patients: Patients using topical corticosteroids should receive the following information and instructions:

1. This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.
2. This medication should not be used for any disorder other than that for which it was prescribed.
3. The treated skin area should not be bandaged or otherwise covered or wrapped so as to be occlusive unless directed by the physician.
4. Patients should report to their physician any signs of local adverse reactions.

Laboratory Tests: The following tests may be helpful in evaluating patients for HPA axis suppression:

ACTH stimulation test

A.M. plasma cortisol test

Urinary free cortisol test

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Two 18-month studies were performed in mice to evaluate the carcinogenic potential of fluticasone propionate when given topically (as an 0.05% ointment) and orally. No evidence of carcinogenicity was found in either study. Fluticasone propionate was not mutagenic in the standard Ames test, *E. coli* fluctuation test, *S. cerevisiae* gene conversion test, or Chinese Hamster ovarian cell assay. It was not clastogenic in mouse micronucleus or cultured human lymphocyte tests.

In a fertility and general reproductive performance study in rats, fluticasone propionate administered subcutaneously to females at up to 50 µg/kg per day and to males at up to 100 µg/kg per day (later reduced to 50 µg/kg per day) had no effect upon mating performance or fertility. These doses are approximately 150 and 300-times, respectively, the human systemic exposure following use of the recommended human topical dose of fluticasone propionate ointment, 0.005%, assuming human percutaneous absorption of approximately 3% and the use in a 70-kg person of 15 g/day.

Studies performed with CUTIVATE Ointment indicate that it is in the medium range of potency as compared with other topical corticosteroids.

INDICATIONS AND USAGE

CUTIVATE Ointment is a medium potency corticosteroid indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

CONTRAINDICATIONS

CUTIVATE Ointment is contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

PRECAUTIONS

General: Systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal from treatment. Manifestations of Cushing's syndrome, hyperglycemia, and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on treatment.

Patients applying a topical steroid to a large surface area or to areas under occlusion should be evaluated periodically for evidence of HPA axis suppression. This may be done by using the ACTH stimulation, A.M. plasma cortisol, and urinary free cortisol tests.

Fluticasone propionate ointment, 0.05% (a concentration 10 times that of fluticasone propionate ointment, 0.005%) suppressed 24-hour urinary free cortisol levels in two of six patients when used at a dose of 30 g/day for a week in patients with psoriasis or atopic eczema. In a second study, fluticasone propionate ointment, 0.05% caused depression of A.M. plasma cortisol levels in 3 of 12 normal volunteers when applied at doses of 50 g/day for 21 days. Morning plasma levels returned to normal levels within the first week upon discontinuation of fluticasone propionate. In this study there was no corresponding decrease in 24-hour urinary free cortisol levels.

If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent corticosteroid. Recovery of HPA axis function is generally prompt upon discontinuation of topical corticosteroids. Infrequently, signs and symptoms of glucocorticosteroid insufficiency may occur, re-

quiring supplemental systemic corticosteroids. For information on systemic supplementation, see prescribing information for those products.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established. Because of a higher ratio of skin surface area to body mass, pediatric patients are at a greater risk than adults of HPA axis suppression and Cushing's syndrome when they are treated with topical corticosteroids. They are therefore also at greater risk of adrenal insufficiency during or after withdrawal of treatment. Adverse effects including striae have been reported with inappropriate use of topical corticosteroids in pediatric patients.

HPA axis suppression, Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hyper-

PRODUCT INFORMATION

SCHERING/2625

INDICATIONS AND USAGE

ELOCON Lotion is indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

CONTRAINDICATIONS

ELOCON Lotion is contraindicated in patients who are hypersensitive to mometasone furoate, to other corticosteroids, or to any ingredient in this preparation.

PRECAUTIONS

General Systemic absorption of potent topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients. Conditions which augment systemic absorption include application of more potent steroids, use over large surface areas, prolonged use, use in areas where the epidermal barrier is disrupted, and the use of occlusive dressings. (See DOSAGE AND ADMINISTRATION.)

Patients receiving a large dose of potent topical steroid applied to a large surface area or under an occlusive dressing should be evaluated periodically for evidence of HPA axis suppression by using the urinary free cortisol and ACTH stimulation tests. If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid.

Recovery of HPA axis function is generally prompt and complete upon discontinuation of the drug. Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids.

Children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity. (See PRECAUTIONS—Pediatric Use.)

If irritation develops, topical corticosteroids should be discontinued and appropriate therapy instituted.

In the presence of dermatological infections, use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, the corticosteroid should be discontinued until the infection has been adequately controlled.

Information for Patients Patients using topical corticosteroids should receive the following information and instructions. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.

Patients should be advised not to use this medication for any disorder other than that for which it was prescribed.

The treated skin area should not be bandaged or otherwise covered or wrapped as to be occlusive unless directed by the physician. (See DOSAGE AND ADMINISTRATION.)

Patients should report any signs of local adverse reactions.

Parents of pediatric patients should be advised not to use the fitting diapers or plastic pants on a child being treated in the diaper area, as these garments may constitute occlusive dressing. (See DOSAGE AND ADMINISTRATION.)

Laboratory Tests The following tests may be helpful in evaluating HPA axis suppression:

Urinary free cortisol test
ACTH stimulation test

Teratogenesis, Mutagenesis, and Impairment of Fertility Long-term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of topical corticosteroids.

Reproductive toxicity studies with mometasone furoate, which included the Ames test, mouse lymphoma assay, and a microtoxicity test, did not reveal any mutagenic potential.

Pregnancy Category C Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. There are no adequate and well-controlled studies of teratogenic effects from topically applied corticosteroids in pregnant women. Therefore, topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Drugs in this class should not be used extensively on pregnant patients in large amounts, or for prolonged periods.

Nursing Mothers It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids are secreted into breast milk in quantities not likely to have a deleterious effect on the infant. Nevertheless, a decision should be made either to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Special Use Pediatric patients may demonstrate greater sensitivity to topical corticosteroid-induced HPA axis suppression and Cushing's syndrome than mature patients due to a larger skin surface area to body weight ratio.

Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema. Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.

ADVERSE REACTIONS

The following local adverse reactions were reported with ELOCON Lotion during clinical studies with 209 patients: acneiform reaction, 2; burning, 4; and itching, 1. In an irritation/sensitization study with 156 normal subjects, folliculitis was reported in 4.

The following local adverse reactions have been reported infrequently when other topical dermatologic corticosteroids have been used as recommended. These reactions are listed in an approximate decreasing order of occurrence: burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, periorificial dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin stroph, striae, miliaria.

OVERDOSAGE

Topically applied corticosteroids can be absorbed in sufficient amounts to produce systemic effects. (See PRECAUTIONS.)

DOSAGE AND ADMINISTRATION

Apply a few drops of ELOCON Lotion to the affected areas once daily and massage lightly until it disappears. For the most effective and economical use, hold the nozzle of the bottle very close to the affected areas and gently squeeze.

HOW SUPPLIED

ELOCON Lotion 0.1% is supplied in 30 mL (27.5 g) (NDC-0085-0854-01) and 60 mL (55 g) (NDC-0085-0854-02) bottles; boxes of one.

Store ELOCON Lotion between 2° and 30°C (36° and 86°F).

Schering Corporation
Kenilworth, NJ 07033 USA

Rev. 1/93

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ELOCON®
brand of mometasone furoate ointment
Ointment 0.1%

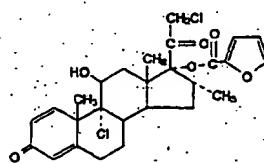
For Dermatologic Use Only
Not for Ophthalmic Use

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DESCRIPTION

ELOCON® (mometasone furoate ointment) Ointment contains mometasone furoate for dermatologic use. Mometasone furoate is a synthetic corticosteroid with anti-inflammatory activity.

Chemically, mometasone furoate is 9a,21-Dichloro-11b,17-dihydroxy-16a-methylpregna-1,4-diene-3,20-dione (17-(2-furoate)), with the empirical formula $C_{21}H_{28}Cl_2O_6$, a molecular weight of 521.4 and the following structural formula:



Mometasone furoate is a white to off-white powder practically insoluble in water, slightly soluble in octanol, and moderately soluble in ethyl alcohol.

Each gram of ELOCON Ointment 0.1% contains: 1 mg mometasone furoate in an ointment base of hexylene glycol, phosphoric acid, propylene glycol stearate, white wax, white petrolatum, and purified water.

CLINICAL PHARMACOLOGY

Like other topical corticosteroids, mometasone furoate has anti-inflammatory, antipruritic, and vasoconstrictive properties. The mechanism of the anti-inflammatory activity of the topical steroids, in general, is unclear. However, corticosteroids are thought to act by the induction of phospholipase A₂ inhibitory proteins, collectively called lipocortins. It

is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A₂.

Pharmacokinetics The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle and the integrity of the epidermal barrier. Occlusive dressings with hydrocortisone for up to 24 hours have not been demonstrated to increase penetration; however, occlusion of hydrocortisone for 96 hours markedly enhances penetration. Studies in humans indicate that approximately 0.7% of the applied dose of ELOCON Ointment 0.1% enters the circulation after 8 hours of contact on normal skin without occlusion. Inflammation and/or other disease processes in the skin may increase percutaneous absorption.

Studies performed with ELOCON Ointment indicate that it is in the medium range of potency as compared with other topical corticosteroids.

In a pediatric trial, 24 atop dermatitis patients, of which 19 patients were age 2 to 12 years, were treated with ELOCON Cream 0.1% once daily. The majority of patients cleared within 3 weeks.

INDICATIONS AND USAGE

ELOCON Ointment 0.1% is a medium potency corticosteroid indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

ELOCON (mometasone furoate ointment) Ointment may be used in pediatric patients 2 years of age or older, although the safety and efficacy of drug use for longer than 3 weeks have not been established (see PRECAUTIONS—Pediatric Use). Since safety and efficacy of ELOCON Ointment have not been established in pediatric patients below 2 years of age, its use in this age group is not recommended.

CONTRAINDICATIONS

ELOCON Ointment is contraindicated in those patients with a history of hypersensitivity to any of the components in the preparation.

PRECAUTIONS

General Systemic absorption of topical corticosteroids can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Manifestations of Cushing's syndrome, hyperglycemia, and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on treatment.

Patients applying a topical steroid to a large surface area or areas under occlusion should be evaluated periodically for evidence of HPA axis suppression. This may be done by using the ACTH stimulation, A.M. plasma cortisol, and urinary free cortisol tests.

In a study evaluating the effects of mometasone furoate ointment on the hypothalamic-pituitary-adrenal (HPA) axis, 15 grams were applied twice daily for 7 days to six adult patients with psoriasis or atop dermatitis. The ointment was applied without occlusion to at least 30% of the body surface. The results show that the drug caused a slight lowering of adrenal corticosteroid secretion.

If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent corticosteroid. Recovery of HPA axis function is generally prompt upon discontinuation of topical corticosteroids. Infrequently, signs and symptoms of glucocorticosteroid insufficiency may occur requiring supplemental systemic corticosteroids. For information on systemic supplementation, see Prescribing Information for those products.

Pediatric patients may be more susceptible to systemic toxicity from equivalent doses due to their larger skin surface to body mass ratios (see PRECAUTIONS—Pediatric Use). If irritation develops, ELOCON Ointment should be discontinued and appropriate therapy instituted. Allergic contact dermatitis with corticosteroids is usually diagnosed by observing failure to heal rather than noting a clinical exacerbation as with most topical products not containing corticosteroids. Such an observation should be corroborated with appropriate diagnostic patch testing.

If concomitant skin infections are present or develop, an appropriate antifungal or antibacterial agent should be used. If a favorable response does not occur promptly, use of ELOCON Ointment should be discontinued until the infection has been adequately controlled.

Information for Patients Patients using topical corticosteroids should receive the following information and instructions:

1. This medication is to be used as directed by the physician.
It is for external use only. Avoid contact with the eyes.

Continued on next page

Information on Schering products appearing on these pages is effective as of August 15, 1997.

2624/SCHERING

PHYSICIANS' DESK REFERENCE

Elocon Cream—Cont.

axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Manifestations of Cushing's syndrome, hyperglycemia, and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on treatment. Patients applying a topical steroid to a large surface area or to areas under occlusion should be evaluated periodically for evidence of HPA axis suppression. This may be done by using the ACTH stimulation, A.M. plasma cortisol, and urinary free cortisol tests.

In a study evaluating the effects of mometasone furoate cream on the hypothalamic-pituitary-adrenal (HPA) axis, 15 grams were applied twice daily for 7 days to six adult patients with psoriasis or atopic dermatitis. The cream was applied without occlusion to at least 30% of the body surface. The results show that the drug caused a slight lowering of adrenal corticosteroid secretion.

If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent corticosteroid. Recovery of HPA axis function is generally prompt upon discontinuation of topical corticosteroids. Infrequently, signs and symptoms of glucocorticosteroid insufficiency may occur requiring supplemental systemic corticosteroids. For information on systemic supplementation, see Prescribing Information for those products.

Pediatric patients may be more susceptible to systemic toxicity from equivalent doses due to their larger skin surface to body mass ratios (see PRECAUTIONS—Pediatric Use). If irritation develops, ELOCON Cream should be discontinued and appropriate therapy instituted. Allergic contact dermatitis with corticosteroids is usually diagnosed by observing a failure to heal rather than noting a clinical exacerbation as with most topical products not containing corticosteroids. Such an observation should be corroborated with appropriate diagnostic patch testing.

If concomitant skin infections are present or develop, an appropriate antifungal or antibacterial agent should be used. If a favorable response does not occur promptly, use of ELOCON Cream should be discontinued until the infection has been adequately controlled.

Information for Patients Patients using topical corticosteroids should receive the following information and instructions:

1. This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.
2. This medication should not be used for any disorder other than that for which it was prescribed.
3. The treated skin area should not be bandaged or otherwise covered or wrapped so as to be occlusive unless directed by the physician.
4. Patients should report to their physician any signs of local adverse reactions.
5. Parents of pediatric patients should be advised not to use ELOCON Cream in the treatment of diaper dermatitis. ELOCON Cream should not be applied in the diaper area as diapers or plastic pants may constitute occlusive dressing (see DOSAGE AND ADMINISTRATION).
6. This medication should not be used on the face, underarms, or groin areas unless directed by the physician.
7. As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 2 weeks, contact the physician.

Laboratory Tests The following tests may be helpful in evaluating patients for HPA axis suppression:

ACTH stimulation test

A.M. plasma cortisol test

Urinary free cortisol test

Carcinogenesis, Mutagenesis, and Impairment of Fertility In studies of the effect of mometasone furoate on fertility, pregnancy, and postnatal development in rats and rabbits, 25 rats were treated with doses up to 1.2 mg/kg of drug topically, and 15 rabbits with doses up to 0.3 mg/kg of drug topically. The drugs were left on the skin for 6 hours daily during gestation. At the highest dosage, the rat dams lost weight. One of the rabbit dams at the highest dosage had wrinkled skin, muscle wasting and aborted 5 fetuses.

Genetic toxicity studies with mometasone furoate, which included the Ames test, mouse lymphoma assay, and a micronucleus test did not reveal any mutagenic potential.

Long term animal studies have not been performed to evaluate the carcinogenic potential of ELOCON (mometasone furoate cream) Cream.

Pregnancy Teratogenic effects: Pregnancy Category C Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application in laboratory animals.

Rat offspring of dams treated with 1.2 mg/kg of mometasone furoate (4 times the maximum dose in a 50 kg individual) displayed umbilical hernias, unossified sternabrae, and vertebrae, and wavy ribs, as well as markedly de-

pressed fetal growth. Rabbit offspring of dams treated with up to 0.3 mg/kg of mometasone furoate topically (the same dose as the maximum dose in a 50 kg individual) displayed flexed paws, umbilical hernias, and cleft palate. A 50 kg female using 1 gram of ELOCON Cream would apply approximately 0.023 mg/kg.

There are no adequate and well-controlled studies of the teratogenic potential of mometasone furoate in pregnant women. ELOCON Cream should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk; caution should be exercised when ELOCON Cream is administered to a nursing woman.

Pediatric Use ELOCON Cream may be used with caution in pediatric patients 2 years of age or older, although the safety and efficacy of drug use for longer than 3 weeks have not been established. Use of ELOCON Cream is supported by results from adequate and well-controlled studies in pediatric patients with corticosteroid-responsive dermatoses. Since safety and efficacy of ELOCON Cream have not been established in pediatric patients below 2 years of age, its use in this age group is not recommended. Because of a higher ratio of skin surface area to body mass, pediatric patients are at a greater risk than adults of HPA axis suppression and Cushing's syndrome when they are treated with topical corticosteroids. They are, therefore, also at greater risk of adrenal insufficiency during and/or after withdrawal of treatment. Pediatric patients may be more susceptible than adults to skin atrophy, including striae, when they are treated with topical corticosteroids. Pediatric patients applying topical corticosteroids to greater than 20% of body surface are at higher risk of HPA axis suppression.

HPA axis suppression, Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in pediatric patients receiving topical corticosteroids. Manifestations of adrenal suppression in children include low plasma cortisol levels, and an absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanels, headaches, and bilateral papilledema.

ELOCON (mometasone furoate cream) Cream should not be used in the treatment of diaper dermatitis.

ADVERSE REACTIONS

In controlled clinical studies involving 319 patients, the incidence of adverse reactions associated with the use of ELOCON Cream was 1.6%. Reported reactions included burning, pruritus, and skin atrophy. Reports of rosacea associated with the use of ELOCON Cream have also been received. In controlled clinical studies (n=74) involving pediatric patients 2 to 12 years of age, the incidence of adverse experiences associated with the use of ELOCON Cream was approximately 7%. Reported reactions included stinging, pruritus, and furunculosis.

The following additional local adverse reactions have been reported infrequently with topical corticosteroids, but may occur more frequently with the use of occlusive dressings. These reactions are listed in an approximate decreasing order of occurrence: irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, periorificial dermatitis, allergic contact dermatitis, secondary infection, striae, and miliaria.

OVERDOSAGE

Topically applied ELOCON Cream can be absorbed in sufficient amounts to produce systemic effects (see PRECAUTIONS).

DOSAGE AND ADMINISTRATION

Apply a thin film of ELOCON Cream to the affected skin areas once daily.

ELOCON Cream may be used in pediatric patients 2 years of age or older. Safety and efficacy of ELOCON Cream in pediatric patients for more than 3 weeks of use have not been established. Use in pediatric patients under 2 years of age is not recommended.

As with other corticosteroids, therapy should be discontinued when control is achieved. If no improvement is seen within 2 weeks, reassessment of diagnosis may be necessary.

ELOCON Cream should not be used with occlusive dressings unless directed by a physician. ELOCON Cream should not be applied in the diaper area if the child still requires diapers or plastic pants as these garments may constitute occlusive dressing.

HOW SUPPLIED

ELOCON Cream 0.1% is supplied in 15 g (NDC 0085-0567-01) and 45 g (NDC 0085-0567-02) tubes; boxes of one.

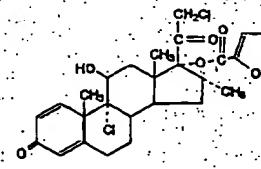
Store ELOCON Cream between 2° and 25°C (36° and 77°F). Schering Corporation Kenilworth, NJ 07033 USA Revised 8/95

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ELOCON®
brand of mometasone furoate
Lotion 0.1%
For Dermatologic Use Only
Not for Ophthalmic Use

DESCRIPTION

ELOCON Lotion 0.1% contains mometasone furoate for dermatologic use. Mometasone furoate is a synthetic corticosteroid with anti-inflammatory activity. Chemically, mometasone furoate is 9a, 21-Dichloro-11b,17a-dihydroxy-16a-methylpregna-1,4-diene-3,20-diene (17a,20a-dihydro-16a-methyl-9a,11b,21-trihydroxy-1,4-dihydro-5a-pregnene-3,20-dione), with the empirical formula $C_{21}H_{29}Cl_2O_5$, a molecular weight of 521.4 and the following structural formula:



Mometasone furoate is a white to off-white powder, only insoluble in water, slightly soluble in ethanol, and moderately soluble in ethyl alcohol. Each gram of ELOCON Lotion 0.1% contains: 1 mg of mometasone furoate in a lotion base of isopropyl alcohol (40%), propylene glycol, hydroxypropylcellulose, sodium phosphate and water. May also contain phosphoric acid and sodium hydroxide used to adjust the pH to approximately 4.5.

CLINICAL PHARMACOLOGY

The corticosteroids are a class of compounds comprising steroid hormones secreted by the adrenal cortex and their synthetic analogs. In pharmacologic doses corticosteroids are used primarily for their anti-inflammatory and/or immunosuppressive effects.

Topical corticosteroids, such as mometasone furoate, are effective in the treatment of corticosteroid-responsive dermatoses primarily because of their anti-inflammatory, and pruritic, and vasoconstrictive actions. However, while the physiologic, pharmacologic, and clinical effects of the corticosteroids are well known, the exact mechanisms of their actions in each disease are uncertain. Mometasone furoate has been shown to have topical (dermatologic) and systemic pharmacologic and metabolic effects characteristic of this class of drugs.

Pharmacokinetics The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressings. (See DOSAGE AND ADMINISTRATION.) Topical corticosteroids can be absorbed from normal intact skin.

A study using a radio-labelled ^3H mometasone furoate ointment (0.1%) formulation was performed in man to measure systemic absorption and excretion. Results showed that approximately 0.7% of the steroid was absorbed during 6 hours of contact, without occlusion, with intact skin of normal volunteers. A similar minimal degree of absorption of the corticosteroid from the lotion formulation would be anticipated.

Inflammation and/or disease processes in the skin increase percutaneous absorption. Occlusive dressings substantially increase the percutaneous absorption of topical corticosteroids. (See DOSAGE AND ADMINISTRATION.)

Mometasone furoate lotion was applied at 15 mg/cm² (30 mL per day) to diseased skin (patients with scalp and body psoriasis) of four patients for seven days, to study the effects on the hypothalamic-pituitary-adrenal (HPA) axis. Plasma cortisol levels for each of the four patients remained well within the normal range and changed little from baseline.

Once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids. Corticosteroids are bound to plasma proteins in varying degrees. Corticosteroids are metabolized primarily in the liver and are then excreted by the kidneys. Some of the topical corticosteroids and their metabolites are also excreted into the bile.

844/DERMIK LABORATORIES

Florone E—Cont.

OVERDOSAGE

Topically applied corticosteroids can be absorbed in sufficient amounts to produce systemic effects. (See PRECAUTIONS.)

DOSAGE AND ADMINISTRATION

Florone E Emollient Cream should be applied to the affected areas as a thin film from one to three times daily depending on the severity or resistant nature of the condition.

Occlusive dressings may be used for the management of psoriasis or recalcitrant conditions.

If an infection develops, the use of occlusive dressings should be discontinued and appropriate antimicrobial therapy initiated.

HOW SUPPLIED

Florone E Emollient Cream is available in the following size tubes:

15 gram NDC 0066-0072-17
30 gram NDC 0066-0072-31
60 gram NDC 0066-0072-60

Store at controlled room temperature, 20° to 25° C (68° to 77° F) [see USP].

Caution: Federal law prohibits dispensing without prescription.

Manufactured by
Pharmacia & Upjohn Company
Kalamazoo, MI, USA 49001

For
Dermik Laboratories, Inc.
A Rhône-Poulenc Rorer Company
Collegeville, PA, USA 19426

Revised June 1996

IN-7154F

813 327 207
691694

HYTONE®

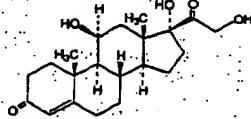
[hi-tōnē]
(hydrocortisone)
Cream, Lotion

DESCRIPTION

Each gram of Hytone® (hydrocortisone) Cream 2 1/2% contains 25 mg of hydrocortisone in a water-washable base of purified water, propylene glycol, glyceryl monostearate SE, cholesterol and related sterols, isopropyl myristate, polysorbate 60, cetyl alcohol, sorbitan monostearate, polyoxy 40 stearate and sorbic acid.

Each mL of Hytone (hydrocortisone) Lotion 2 1/2% contains 25 mg of hydrocortisone in a vehicle consisting of carbomer 940, propylene glycol, polysorbate 40, propylene glycol stearate, cholesterol and related sterols, isopropyl myristate, sorbitan palmitate, cetyl alcohol, triethanolamine, sorbic acid, aminethicone, and purified water.

Chemically, hydrocortisone is [Pregn-4-ene-3,20-dione, 11,17,21-trihydroxy-, (11β)-] with the molecular formula $C_{21}H_{28}O_5$ and is represented by the following structural formula:



Its molecular weight is 362.47 and its CAS Registry Number is 50-23-7. The topical corticosteroids, including hydrocortisone, constitute a class of primarily synthetic steroids used as anti-inflammatory and antipruritic agents.

CLINICAL PHARMACOLOGY

Topical corticosteroids share anti-inflammatory, antipruritic, and vasoconstrictive actions. The mechanism of anti-inflammatory activity of the topical corticosteroids is unclear. Various laboratory methods, including vasoconstrictor assays, are used to compare and predict potencies and/or clinical efficacies of the topical corticosteroids. There is some evidence to suggest that a recognizable correlation exists between vasoconstrictor potency and therapeutic efficacy in man.

Pharmacokinetics: The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressings.

Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption. Occlusive dressings substantially increase the percutaneous absorption of topical corticosteroids. Thus, occlusive dressings may be a valuable therapeutic adjunct for treatment of resistant dermatoses. (See DOSAGE AND ADMINISTRATION.)

Information will be superseded by supplements and subsequent editions

Once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids. Corticosteroids are bound to plasma proteins in varying degrees. Corticosteroids are metabolized primarily in the liver and are then excreted by the kidneys. Some of the topical corticosteroids and their metabolites are also excreted into the bile.

INDICATIONS AND USAGE

Topical corticosteroids are indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

CONTRAINDICATIONS

Topical corticosteroids are contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

PRECAUTIONS

General: Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients.

Conditions which augment systemic absorption include the application of the more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings.

Therefore, patients receiving a large dose of a potent topical steroid applied to a large surface area or under an occlusive dressing should be evaluated periodically for evidence of HPA axis suppression by using the urinary free cortisol and ACTH stimulation tests. If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid.

Recovery of HPA axis function is generally prompt and complete upon discontinuation of the drug. Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids.

Children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity (see Pediatric Use).

If irritation develops, topical corticosteroids should be discontinued and appropriate therapy instituted.

In the presence of dermatological infections, the use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, the corticosteroid should be discontinued until the infection has been adequately controlled.

Information for the Patient: Patients using topical corticosteroids should receive the following information and instructions:

1. This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.
2. Patients should be advised not to use this medication for any disorder other than for which it was prescribed.
3. The treated skin area should not be bandaged or otherwise covered or wrapped as to be occlusive unless directed by the physician.
4. Patients should report any signs of local adverse reactions, especially under occlusive dressing.
5. Parents of pediatric patients should be advised not to use tight-fitting diapers or plastic pants on a child being treated in the diaper area, as these garments may constitute occlusive dressings.

Laboratory Tests: The following tests may be helpful in evaluating the HPA axis suppression:

Urinary free cortisol test

ACTH stimulation test

Carcinogenesis, Mutagenesis and Impairment of Fertility: Long-term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of topical corticosteroids.

Studies to determine mutagenicity with prednisolone and hydrocortisone have revealed negative results.

Pregnancy: Teratogenic Effects: Pregnancy Category C: Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. There are no adequate and well-controlled studies in pregnant women on teratogenic effects from topically applied corticosteroids. Therefore, topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.

Nursing Mothers: It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids are secreted into breast milk in quantities not likely to have a deleterious effect on the infant. Nevertheless, caution should be exercised when topical corticosteroids are administered to a nursing woman.

PHYSICIANS' DESK REFERENCE®

Pediatric Use: Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced HPA axis suppression and Cushing's syndrome than mature patients because of a larger skin surface area to body weight ratio. Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, and intracranial hypertension have been reported in pediatric patients receiving topical corticosteroids. Manifestations of adrenal suppression in pediatric patients include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Administration of topical corticosteroids to pediatric patients should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of pediatric patients.

ADVERSE REACTIONS

The following local adverse reactions are reported infrequently with topical corticosteroids, but may occur more frequently with the use of occlusive dressings. These reactions are listed in an approximate decreasing order of occurrence: burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, periorificial dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae, and miliaria.

OVERDOSAGE

Topically applied corticosteroids can be absorbed in sufficient amounts to produce systemic effects (see PRECAUTIONS).

DOSAGE AND ADMINISTRATION

Topical corticosteroids are generally applied to the affected area as a thin film from two to four times daily depending on the severity of the condition. Occlusive dressings may be used for the management of psoriasis or recalcitrant conditions.

If an infection develops, the use of occlusive dressings should be discontinued and appropriate antimicrobial therapy instituted.

HOW SUPPLIED

Cream-2 1/2% Tube 1 OZ NDC 0066-0095-01;
2 1/2% Tube 2 OZ NDC 0066-0095-02

Lotion-2 1/2% bottle 2 FL OZ NDC 0066-0098-02

Caution: Federal law prohibits dispensing without prescription.

Keep out of the reach of children.

Marketed by
Dermik Laboratories, Inc.
A Rhône-Poulenc Rorer Company
Collegeville, PA 19426

Rev. 12/96

IN-7245D

HYTONE®

[hi-tōnē]
(hydrocortisone)
Ointment

DESCRIPTION

The topical corticosteroids constitute a class of primarily synthetic steroids used as anti-inflammatory and antipruritic agents. Hytone® 2 1/2% (hydrocortisone ointment, USP) contains Hydrocortisone, [Pregn-4-ene-3,20-dione, 11,17,21-trihydroxy-, (11β)-], with the molecular formula $C_{21}H_{28}O_5$ and a molecular weight of 362.47. Each gram of the ointment contains 25 mg of hydrocortisone in a base of white petrolatum and mineral oil.

CLINICAL PHARMACOLOGY

Topical corticosteroids share anti-inflammatory, antipruritic, and vasoconstrictive actions.

The mechanism of anti-inflammatory activity of the topical corticosteroids is unclear. Various laboratory methods, including vasoconstrictor assays, are used to compare and predict potencies and/or clinical efficacies of the topical corticosteroids. There is some evidence to suggest that a recognizable correlation exists between vasoconstrictor potency and therapeutic efficacy in man.

Pharmacokinetics: The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressings.

Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption. Occlusive dressings substantially increase the percutaneous absorption of topical corticosteroids. Thus, occlusive dressings may be a valuable therapeutic adjunct for treatment of resistant dermatoses. (See DOSAGE AND ADMINISTRATION.)

Once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids. Corticosteroids are